Influence of drug-polymer ratio on physical characteristics and release of metformin hydrochloride from metformin-alginate microspheres

by Dewi Melani Hariyadi

Submission date: 11-Jun-2019 12:08PM (UTC+0800)
Submission ID: 1142410305
File name: C-02.pdf (186.29K)
Word count: 3286
Character count: 17588

Tropical Journal of Pharmaceutical Research July 2018; 17 (7): 1229-1233
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v17i7.1

Original Research Article

Influence of drug-polymer ratio on physical characteristics and release of metformin hydrochloride from metformin-alginate microspheres

Dewi Melani Hariyadi*, Esti Hendradi, Tristiana Erawati, Edlin Nur Jannah, Wenny Febrina

Faculty of Pharmacy, Pharmaceutics Department, Universitas Airlangga, Surabaya, Indonesia

For correspondence:* ***Email:* *dewi-m-h@ff.unair.ac.id;* ***Tel:*** *+62 31 5033710;* ***Fax:*** *+62 31 5022514*

Sent for review: 25 February 2018 *Revised accepted: 18 June 2018*

Abstract

Purpose: *To investigate the effect of drug and polymer ratio on the physical characteristics and release rate of metformin hydrochloride from alginate microspheres.*

Methods: *Microspheres were prepared by ionotropic gelation aerosolization technique using sodium alginate as polymer and calcium chloride as crosslinker. Three formulations of drug and alginate polymer ratios: 1:1 (F1); 1:1.5 (F2); and 1:2 (F3), and 10 % calcium chloride ($CaCl_2$) were investigated. The microspheres were studied with respect to physical characteristics, release profile and release rate. Release evaluation was done at pH 1.2 in hydrochloric acid (HCl) for 2 h, and in phosphate-buffered saline (PBS) at pH 7.4 for 12 h.*

Results: *Drug loading in formulations F1, F2 and F3 were 3.08 ± 0.21, 3.34 ± 0.28, and 3.99 ± 0.19 %, respectively. Low entrapment of below 15 % was achieved for all formulations, whereas high yield (above 45 %) was obtained. Drug release above 74 % was observed for all formulations. The release rates of F1, F2 and F3 were 9.6390 x 10-2, 9.0985 x 10^{-2}, and 8.3312 x 10^{-2} %/min, respectively.*

Conclusion: *Metformin-alginate microspheres can be used for optimized formulations with good physical characteristics and in vitro release. These findings suggest that the microspheres might be a potent drug delivery system for the treatment of diabetic mellitus.*

Keywords: *Metformin, Alginate microspheres, Drug-polymer ratio, Aerosolization, Drug release*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Diabetes is a chronic metabolic disease characterized by high fasting blood sugar levels [1]. Metformin hydrochloride (metformin HCl) is a biguanide drug used for treating non-insulin dependent diabetes mellitus [2,3]. However, metformin HCl has a short half-life of about 2.7 to 4 h, thereby necessitating frequent administration to patients for control of blood glucose [4,5]. One way of solving this problem is by encapsulating the drug in the microsphere delivery system to prolong its half-life and minimize its side effects [6].

Microspheres are drug-containing matrix systems with sizes in the range 5 - 5000 µm, and are usually used for slow and controlled-release [7,8]. Ionotropic gelation is a simple, quick and cost-effective method which is able to crosslink to counter ions to form hydrogel using drop or aerosolization [9,10]. Alginate is an anionic, biocompatible and biodegradable polysaccharide comprising L-glucuronic (G) and D-mannuronic acid (M) subunits [11-14]. Alginate forms egg-box gels with a divalent cation such as Ca^{2+} [13]. Microsphere formulations are influenced by factors such as drug, polymer and cross-linker concentrations; cross-link time and ratio of drug to polymer [15]. Some studies used polymer : drug ratios of 1:1, 1:1.5 and 1:2 to improve the entrapment efficiency of metformin HCL from 66.7 to 85.08 % [13,16,17]. However, the size of the microspheres produced was still large (100 - 480 µm). Therefore, there is need for optimal polymer and drug concentrations [18]. To improve their stability, microspheres have been formulated in dry forms using freeze drying and maltodextrin as lyoprotectant [19,20]. The aim of the present study was to investigate the effect of drug : polymer ratios on the physical characteristics and release of metformin HCl from alginate microspheres.

EXPERIMENTAL

Materials

Metformin HCl was product of Combiphar; sodium alginate was obtained from Sigma-Aldrich Inc.; while food grade $CaCl_2H_2O$, sodium citrate, maltodextrin and aquadest were products of PT.Bratachem. Hydrochloric acid, Na_2HPO_4, KH_2PO_4, phosphate buffered saline (PBS), NaOH and NaCl were supplied by Merck). Metformin, sodium alginate and citrate were pharmaceutical grade.

Formulation of microspheres

The production of metformin HCl-alginate microspheres using aerosolization technique was started by dissolving Na Alginate in 100 ml distilled water to yield 0.5, 0.75 and 1.0 % solutions. Metformin HCl (500 mg) was then dispersed into the resultant alginate solutions, and mixed until homogeneous. A solution of $CaCl_2$ was made in 100 mL of aquadest according to the concentration in the formula. Each dispersed solution of metformin HCl-alginate was sprayed into the $CaCl_2$ solution using a spray aerosol of aperture 5 µm at a constant pressure of 40 psi. The distance between the atomizer and the surface of the $CaCl_2$ solution was maintained at 8 cm, and the sprayed mixture was stirred with a magnetic stirrer for 30 min at 1000 rpm. The resultant microspheres were separated from the $CaCl_2$ by centrifugation at 2500 rpm for 6 min, washed twice with aquadest, and suspended in 5 % maltodextrin lyoprotectant. Finally, the microspheres were freeze-dried at - 80 °C for 29 h. The compositions of the various microspheres are shown in Table 1.

Table 1: Compositions of metformin HCl-alginate microspheres

Ingredient	Function	F1 1:1	F2 1:1.5	F3 1:2
Metformin HCl (mg)	Active agent	500	500	500
Na Alginate (mg)	Polymer	500	750	1000
$CaCl_2$ (%)	Crosslinker	10	10	10
Crosslinking time (min)	-	30	30	30
Maltodextrin (%)	Lyoprotectant	5	5	5

Formulation F1: Metformin HCl-alginate microspheres with drug: polymer ratio 1:1
Formulation F2: Metformin HCl-alginate microspheres with drug: polymer ratio 1:1.5
Formulation F3: Metformin HCl-alginate microspheres with drug: polymer ratio 1:2

Evaluation of entrapment efficiency and drug loading

Microspheres (150 mg) were added to 50 ml of 0.5 M Na Citrate buffer, pH 7. The mixture of microspheres and Na Citrate was stirred using a magnetic stirrer at 1000 rpm for 3 h, and the absorbance of the sample solution was read in a spectrophotometer at 239 nm. The entrapment efficiency was calculated from the content of metformin HCl in microspheres as the ratio of metformin HCl to theoretical content of metformin HCl expressed as a percentage, while drug loading was computed as the ratio of the weight of the dry microspheres to the weight of the initial microspheres expressed as a percentage.

Determination of yield

The yield of microspheres was calculated as the ratio of the dry microsphere to the total weight of the ingredients used in producing the dry microspheres.

Morphological examination

The morphology of the metformin HCl-Alginate microspheres were evaluated using an optical microscope, while that of the dry microspheres

was observed with a scanning electron microscope (SEM).

In vitro drug release studies

In vitro drug release studies were conducted by first constructing a standard curve of metformin HCl in HCl at pH 1.2, and in PBS at pH 7.4. Metformin HCl release from microspheres was studied in a thermoshaker at 37 °C at a speed of 100 rpm. Each formulation of microspheres weighed 750 mg. This was added to the release medium. The release medium (100 ml of HCl, pH 1.2) was prepared and thermostated at 37 ± 0.5 °C. Once the temperature reached 37 ± 0.5 °C and speed was set up at 100 rpm, samples of the HCl medium, pH 1.2 were removed at the rate of 3.0 ml/min at 10, 30, 60, and 120 min. Each withdrawn sample was replaced with an equivalent volume of the release medium at the same temperature. Then, the pH of the medium was adjusted to 7.4 by adding 10.597 grams Na_2HPO_4; $2PO_4$ 1.499 gram, and 2.4 ml of 3 N NaOH. Thereafter, samples were withdrawn from the new release medium of pH 7.4 at 130, 180, 240, 360, 480, 600 and 720 min. the samples taken were replaced with phosphate buffered saline (PBS) pH 7.4 ± 0.05 at the same temperature. The samples were filtered through a filter paper (0.45 µm pore), and their absorbance was read at 232 nm in a spectrophotometer. The Metformin HCl concentrations were obtained from the standard curve regression equation of metformin HCl solution at 232 nm

Statistical analysis

Drug loading, entrapment efficiency and yield were analyzed statistically using one way analysis of variance (ANOVA) with IBM SPSS Statistic 22.0 program at 95 % confidence level.

RESULTS

Optical microscopy of the morphology of the wet microspheres F1, F2 and F3 showed spherical shape and smooth surfaces. The addition of maltodextrin as cryoprotectant resulted in microspheres with a spherical shape and a smooth surface. This was also evident from the results of SEM on the dry microspheres (Figure 1).

Data on drug loadings of metformin HCl in microspheres, entrapment efficiency and yield are presented in Table 2. The flux of metformin HCl from microspheres, and their release profiles at pH 1.2 and pH 7.4 are shown in Table 3 and Figure 2, respectively.

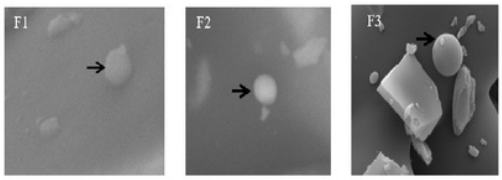

Figure 1: Morphologies of dry microspheres as seen using SEM

Table 2: Entrapment efficiency, drug loading and yield in the microsphere formulations

Formulation	Metformin loading	Entrapment efficiency	Yield
F1	3.08 ± 0.21	6.70 ± 0.20	47.69 ± 6.33
F2	3.34 ± 0.28	9.66 ± 0.42	58.91 ± 3.30
F3	3.99 ± 0.19	13.63 ± 0.21	65.46 ± 5.72

Table 3: Release rate (flux) of metformin HCl from the microspheres

Formulation	Mean slope ± SD
F1	$9.6390 \times 10^{-2} \pm 0.9077 \times 10^{-2}$
F2	$9.0985 \times 10^{-2} \pm 3.1949 \times 10^{-2}$
F3	$8.3312 \times 10^{-2} \pm 2.0656 \times 10^{-2}$

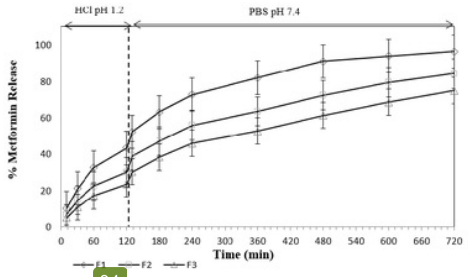

Figure 2: Release profiles of metformin HCl from the microspheres in solution pH 1.2 and 7.4

DISCUSSION

In this study, the addition of maltodextrin resulted in the spherical shape and smooth surface of the microspheres. This was due the covering of cavities or pores on the surface of the microspheres, thus increasing their number and size through the formation of hydrogen bonds with polar groups on the surface of microspheres [20]. The amorphous form of maltodextrin maximized the number of hydrogen bonds formed [20,22]. The particle size of microspheres was about 3 µm in the three formulations.

Results of loadings, entrapment efficiency and yield showed that metformin HCl loading in microspheres increased in response to increases in alginate polymer levels. This was so because increased levels of alginate enhanced the degree of cross-links, thereby increasing the availability of calcium binding sites in the polymer chain, and hence the capacity of the microspheres to bind the drug [21,23]. In addition, increases in polymer: drug ratios enhanced entrapment efficiency because an increase in polymer increases the encapsulation of metformin HCl [25]. Thus, the entrapment efficiency of F3 was greater than that of F2 or F1.

The yield of the three formulations suggested that increased polymer concentration enhanced microsphere yield. Following evaluations of drug loadings and entrapment efficiency, further experiments on release testing was conducted. The release rate study was performed in two phases because the release was made to mimic physiological conditions. In the first phase, microspheres were incubated in HCl at pH 1.2 for 120 min. Conditions in this first phase resembled those of the stomach, where gastric pH during fasting reaches 1 – 2, with gastric emptying time of about 2 - 6 h, depending on the amount and type of food consumed. After sampling for 120 min, the pH of the HCl medium was adjusted to 7.4 ± 0.5, to mimic the pH of the intestine, and used to evaluate metformin HCl release at alkaline pH. The cumulative percentage release of metformin HCl for 12 h from F1, F2 and F3 were 96.40 ± 7.37, 84.27 ± 13.96, and 74.98 ± 12.95 %, respectively.

Based on results obtained from release profile were in accordance with the hypothesis at the outset that amount of metformin hydrochloride were separated at acidic pH and amount of drug were loose at alkaline pH was greater and constantly released within certain time.

It has been reported that an increase in polymer concentration increased the entrapment capacity of drugs in microspheres [21]. Increasing concentrations of alginate microspheres will lead to slower release because the surface of microspheres becomes coated with polymer, leading to slower diffusion of drug out of the matrix [25]. The rate of release was obtained by regression at steady state conditions. The slope of the regression equation showed the rate of release (flux) of metformin HCl from the alginate microspheres. The flux of F1, F2 and F3 were 9.6390×10^{-2}, 9.0985×10^{-2}, and 8.3312×10^{-2} %/min, respectively. These results indicated a trend in which increased concentrations of alginate decreased the release rate of metformin HCl. When the concentration of alginate is increased, the thickness of the layer around drug particles is also increased [21]. A decrease in the release rate of a drug may occur as a result a decrease in the diffusion coefficient of the drug, the pore size of particles and the rate of particle swelling in body fluids so that the penetration rate of body fluids into the particle decreases [21,25]. Statistically significant differences were seen in the metformin HCl release rates of F1, F2 and F3. This may be caused a number of factors: the concentration of the polymer used was probably not enough for optimal crosslinker levels. Moreover, it is possible that the crosslinking time, and the stirring speed were not optimal. Metformin HCl-alginate microsphere preparation by ionotropic gelation method at drug : polymer ratios of 1: 1; 1: 1.5; and 1: 2 did not provide significant differences in the release rates. Thus, further research to improve drug loadings and *in vivo* tests were needed.

CONCLUSION

This research has formulated optimized metformin-alginate microspheres and showed their good physical characteristics and *in vitro* drug release profiles. These findings suggest that the microspheres might be potent drug delivery systems for the treatment of diabetic mellitus.

DECLARATIONS

Acknowledgement

The authors would like to thank Universitas Airlangga and the Faculty of Pharmacy for providing laboratory facilities for the studies.

Conflict of interest

No conflict of interest is associated with this work.

Author contribution

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

REFERENCES

1. *Sutar PS, Sutar KP, Sambrekar AS, Patil VS, Kudalagi CR. Formulation and Evaluation of Metformin Hydrochloride Chitosan Loaded Microspheres. J Pharm Sci Innov 2012; 1(2):12-16.*

2. Zhao L, Yumeng W, Yong M, Li Y, Yuan Y, Xufeng Y, Yanhong J. Preparation and in Vitro Drug Release Evaluation of Once-Daily Metformin Hydrochloride Sustained-Release Tablets. J. Pharm. Pharmacol. 2012; 3: 468-473.
3. Halimi S, Debaty I, Villaret L, Muller M. New therapies for type 2 diabetic: What place for incretin-based agents and rimonabant compared to the previous ones?. Rev Med Interne 2008; 29: 881–890.
4. Brunton LL, Chabner BA, Knollmann BC. Goodman & Gilman's The Pharmacological Basis of Therapeutics. Columbus: McGraw Hill; 2011.
5. Robert F, Fendri S, Hary L, Lacroix C, Andrejak M, Lalau JD. Kinetics of plasma and erythrocyte metformin after acute administration in healthy subjects. Diabetic Metab 2003; 29: 279–283.
6. Liu H, Su XY, Li X, Zhao X, Zang L, Pan WS. Development of Prolonged Release Microspheres of Metformin Hydrochloride Using Ion Exchange Resins. J Chinese Pharm Sci 2006; 15(3): 155-161.
7. Murtaza G, Ahamd M, Akhtar N, Rasool F. A Comparative Study Of Various Microencapsulation Techniques: Effect Of Polymer Viscosity On Microcapsule Characteristics. Pak J Pharm Sci 2009; 22(3): 291-300.
8. Burgess DJ, Hickey AJ. Microspheres Technology and Applications. In: J. Swarbrick, and J.C. Boylan (Eds.). Encyclopedia of Pharmaceutical Technology, Ed. 3rd. New York: Informa Healthcare USA Inc. 2007; 2328-2338.
9. Hariyadi DM, Hendradi E, Piay OLV, Ramadani CN. 2013. Optimasi Mikrosfer Ovalbumin-Alginat Yang Diproduksi Dengan Teknik Aerosolisasi. PharmaScientia 2013; 2 (1): 21-30.
10. Agnihotri SA, Nadagouda N, Mallikarjuna TM, Aminabhavi. Review: Recent Advances on Chitosan Based Micro and Nanoparticles in Drug Delivery. J Control Release 2004; 100: 5–28.
11. Yang JS, Xie YJ, He W. Research Progress on Chemical Modification of Alginate: A Review. Carbohydrate Polymers 2011; 84(1): 33–39.
12. Lee KY, Mooney DJ. Alginate: Properties And Biomedical Applications. Prog Polym Sci 2012; 37(1): 106–126.
13. Balasubramaniam J, Rao VU, Vasudha M, Babu J, Rajinikanth PS. Sodium Alginate Microspheres of Metformin HCl: Formulation and In Vitro Evaluation. Curr Drug Deliv 2007; 4: 249-256.
14. Dong S, Yang J, Zhang XY, Shi M, Song XY, Chen XL, Zhang YZ. Cultivable Alginate Lyase-Excreting Bacteria Associated with the Arctic Brown Alga Laminaria. Mar Drugs 2012; 10: 2481-2491.
15. Tello F, Cortes RNF, Bustos FM, Silva VM, Hubinger MD, Grosso C. Alginate and pectin-based particles coated with globular proteins: Production, characterization and anti-oxidative properties. Food Hydrocoll 2015; 43: 670-678.
16. Mittal A, Singh A, Maiti A. Comparative Study of Alginate and Pectin Sustained Release Floating Beads of Metformin Hydrochloride. Pharma Research 2013; 8(2):23-30.
17. Yaddalapudi S, Palla G. Formulation and Evaluation of Metformin Hydrochloride Sustained Released Microspheres. J Compr Phar 2014; 1(4):136-141.
18. Islan GA, Verti IP, Marchetti SG, Castro GR. Studies of Ciprofloxacin Encapsulation on Alginate/Pectin Matrixes and Its Relationship with Biodisponibility. Appl Biochem Biotechnol 2012; 167: 1408-1420.
19. Hariyadi DM, Purwanti T, Kusumawati I, Nirmala RN, Maindra HMC. Physical Characterization and In Vivo Study of Ovalbumin Encapsulated in Alginate Microspheres. IJDDT 2015; 5(2); 48-53.
20. Abdelwahed W, Degobert G, Stainmesse S, Fessi H. Freeze-Drying of Nanoparticles: Formulation, Process and Storage Considerations. Adv Drug Del Rev 2006; 58: 1688–1713.
21. Zafar A, Bhattacharyya A, Bajpai M, Yasir M, Asif M. Formulation and In vitro Characterization of Floating Gel Beads of Metformin Hydrochloride, Int J Pharm Sci Nanotechnol 2014; 7(1): 2356-2362.
22. Elnaggar YS, El-Massik MA, Abdallah OY, Ebian AE. Maltodextrin: a novel excipient used in sugar-based orally disintegrating tablets and phase transition process. AAPS PharmSciTech 2010; 11(2): 645-651.
23. Mandal U, Gowda V, Ghosh A, Selvan S, Solomon S, Pal TK. Formulation and optimization of sustained release matrix tablet of metformin HCl 500 mg using response surface methodology. Yakugaku Zasshi. 2007; 127(8): 1281-1290.
24. Garud N, Garud A. Preparation and In-vitro Evaluation of Metformin Microspheres Using Non-Aqueous Solvent Evaporation Technique. Trop J Pharm Res 2012; 11 (4): 577-583.
25. Joshi S, Patel P, Lin S, Mada PL. Development of cross-linked alginate spheres by ionotropic gelation technique for controlled release of naproxen oral. Asian J Pharm 2012; 7(2): 134-142.

Influence of drug-polymer ratio on physical characteristics and release of metformin hydrochloride from metformin-alginate microspheres

ORIGINALITY REPORT

14%	7%	12%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ijppsjournal.com Internet Source	1%
2	Zhang, Xian-Zhao, Fu-Jun Tian, Ya-Min Hou, and Zhi-Hong Ou. "Preparation and in vitro in vivo characterization of polyelectrolyte alginate–chitosan complex based microspheres loaded with verapamil hydrochloride for improved oral drug delivery", Journal of Inclusion Phenomena and Macrocyclic Chemistry, 2015. Publication	1%
3	de.scribd.com Internet Source	1%
4	"Abstracts for 6th Central European Symposium on Pharmaceutical Technology and Biotechnology", European Journal of Pharmaceutical Sciences, 200505 Publication	1%

5	Sharad Visht, GT Kulkarni. "Studies on the preparation and in vitro - in vivo evaluation of mucoadhesive microspheres of glycyrrhetinic acid isolated from liquorice", Bangladesh Pharmaceutical Journal, 2015 Publication	1%
6	Lopedota, A., A. Cutrignelli, A. Trapani, G. Boghetich, N. Denora, V. Laquintana, G. Trapani, and G. Liso. "Effects of different cyclodextrins on the morphology, loading and release properties of poly (DL-lactide-co-glycolide)-microparticles containing the hypnotic agent etizolam", Journal of Microencapsulation, 2007. Publication	<1%
7	www.eurostar-science.org Internet Source	<1%
8	ddtjournal.com Internet Source	<1%
9	jacobspublishers.com Internet Source	<1%
10	Hannah C. Bygd, Kaitlin M. Bratlie. "The effect of chemically modified alginates on macrophage phenotype and biomolecule transport", Journal of Biomedical Materials Research Part A, 2016 Publication	<1%

11	Mohammed, Fergany A., and Hussin Khedr. "Preparation and In Vitro/In Vivo Evaluation of the Buccal Bioadhesive Properties of Slow-Release Tablets Containing Miconazole Nitrate", Drug Development and Industrial Pharmacy, 2003. Publication	<1%
12	DongKyu Sohn, K. Hirasawa, Jinglu Hu. "Adaptive Random Search with Intensification and Diversification combined with Genetic Algorithm", 2005 IEEE Congress on Evolutionary Computation, 2005 Publication	<1%
13	Sheshala, Ravi, Nurzalina Khan, and Yusrida Darwis. "Formulation and Optimization of Orally Disintegrating Tablets of Sumatriptan Succinate", CHEMICAL & PHARMACEUTICAL BULLETIN, 2011. Publication	<1%
14	academic.oup.com Internet Source	<1%
15	repository.upi.edu Internet Source	<1%
16	repository.unair.ac.id Internet Source	<1%
	Sana Ghayas, Muhammad Harris Shoaib,	

17	Faaiza Qazi, Rabia Bushra, Fatima Ramzan Ali, Madiha Maboos, Farah Khalid. "Influence of different viscosity grade cellulose-based polymers on the development of valsartan controlled release tablets", Polymer Bulletin, 2019 Publication	<1%
18	R. B. Umamaheswari. "Floating-Bioadhesive Microspheres Containing Acetohydroxamic Acid for Clearance of Helicobacter Pylori", Drug Delivery, 10/1/2002 Publication	<1%
19	Emine Bulut, Oya Oya Sanli. "Delivery of Alzheimer's Drug Donepezil Hydrochloride from Ionically Crosslinked Alginate Microspheres Prepared by Water-in-oil Emulsion Technique: Optimization of Release Conditions", Asian Journal of Chemistry, 2013 Publication	<1%
20	Comoglu, T.. "Preparation and in vitro evaluation of modified release ketoprofen microsponges", Il Farmaco, 200302 Publication	<1%
21	Argia Acarregui, Ainhoa Murua, José L. Pedraz, Gorka Orive, Rosa M. Hernández. "A Perspective on Bioactive Cell Microencapsulation", BioDrugs, 2012 Publication	<1%

22	www.apjonline.in Internet Source	<1%
23	Tiyaboonchai, W.. "Formulation and characterization of DNA-polyethylenimine-dextran sulfate nanoparticles", European Journal of Pharmaceutical Sciences, 200307 Publication	<1%
24	Anil K. Anal, Deepak Bhopatkar, Seiichi Tokura, Hiroshi Tamura, Willem F. Stevens. "Chitosan-Alginate Multilayer Beads for Gastric Passage and Controlled Intestinal Release of Protein", Drug Development and Industrial Pharmacy, 2003 Publication	<1%
25	www.ijpcsonline.com Internet Source	<1%
26	Wu, Baojian, Ningyun Shun, Xiuli Wei, and Wei Wu. "Characterization of 5-Fluorouracil Release from Hydroxypropylmethylcellulose Compression-Coated Tablets", Pharmaceutical Development and Technology, 2007. Publication	<1%
27	Bulut, Emine. "Ibuprofen microencapsulation within acrylamide-grafted chitosan and methylcellulose interpenetrating polymer network microspheres: Synthesis,	<1%

characterization, and release studies", Artificial Cells Nanomedicine and Biotechnology, 2015.
Publication

28	Bravo, Silvina A., Maria C. Lamas, and Claudio J. Salomon. "Swellable Matrices for the Controlled-Release of Diclofenac Sodium: Formulation and In Vitro Studies", Pharmaceutical Development and Technology, 2004. Publication	<1%
29	Yen, S.Y.. "Controlled release of nalbuphine propionate from biodegradable microspheres: in vitro and in vivo studies", International Journal of Pharmaceutics, 20010604 Publication	<1%
30	repositories.lib.utexas.edu Internet Source	<1%
31	www.dissolutiontech.com Internet Source	<1%
32	N. Bolourtchian, K. Karimi, R. Aboofazeli. "Preparation and characterization of ibuprofen microspheres", Journal of Microencapsulation, 2008 Publication	<1%
33	Fabián Martínez-Gómez, Juan Guerrero, Betty Matsuhiro, Jorge Pavez. "In vitro release of metformin hydrochloride from sodium	<1%

alginate/polyvinyl alcohol hydrogels", Carbohydrate Polymers, 2017
Publication

---

34 John Rojas, Cesar González, Carolina Rico, Oswaldo Saez. "Formulation of a modified release metformin. HCl matrix tablet: influence of some hydrophilic polymers on release rate and in-vitro evaluation", Brazilian Journal of Pharmaceutical Sciences, 2011 <1%
Publication

---

35 Murtaza, Ghulam, Mahmood Ahmad, Shujaat Khan, and Izhar Hussain. "Evaluation of Cefixime-Loaded Chitosan Microspheres: Analysis of Dissolution Data Using DDSolver", Dissolution Technologies, 2012. <1%
Publication

Exclude quotes	Off	Exclude matches	Off
Exclude bibliography	On		